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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket Nos. 76N–0080 and 00N–1610]

RIN 0910–AC12

Digoxin Products for Oral Use; Revocation of Conditions for Marketing

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revoking the regulation establishing conditions for marketing digoxin products for oral use. This regulation is no longer necessary because the products, which are new drugs, can be regulated under the approval process for new drug applications (NDAs) and abbreviated new drug applications (ANDAs) as set forth in the Federal Food, Drug, and Cosmetic Act (the act).

DATES: This rule is effective [*insert date 30 days after date of publication in the* **Federal Register**]. FDA does not plan to take regulatory action against currently marketed unapproved digoxin elixir products before [*insert date 2 years after date of publication in the* **Federal Register**]. Any unapproved digoxin elixir introduced after [*insert date of publication in the* **Federal Register**], will be subject to regulatory action on [*insert date 30 days after date of publication in the* **Federal Register**]. Any unapproved digoxin tablet will be subject to regulatory action on [*insert date 30 days after date of publication in the* **Federal Register**].

FOR FURTHER INFORMATION CONTACT: Mary E. Catchings, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 24, 2000 (65 FR 70538), FDA proposed to revoke § 310.500 (21 CFR 310.500), which established conditions for marketing digoxin products for oral use (tablets and elixir). The regulation: (1) Declared all digoxin products for oral use (tablets and elixir) to be new drugs, (2) required submission of ANDAs and bioavailability tests for all oral digoxin products (the requirement for the submission of ANDAs was stayed indefinitely (41 FR 43135, September 30, 1976)), (3) required a mandatory FDA certification program for digoxin tablets based on dissolution testing by the National Center for Drug Analysis, (4) required a recall of any previously marketed batch of digoxin tablets found to fail United States Pharmacopeia (USP) dissolution specifications, and (5) set forth a labeling requirement for all oral digoxin products.

In the preamble to the proposed rule, FDA described actions that have occurred since § 310.500 was published that render the regulation unnecessary. The agency discussed the 1997 approval of NDA 20–405 for Lanoxin (digoxin) Tablets and described the indications for the tablets, which differ from the indications for oral digoxin drug products set forth in § 310.500. The agency explained that because of the approval of NDA 20–405, digoxin tablets are now eligible for ANDAs under section 505 of the act (21 U.S.C. 355).

The agency also noted that the dissolution requirements specified in § 310.500 are no longer used as standards in the certification program and are therefore obsolete. The agency concluded that regulation of these products under batch certification was no longer warranted.

The proposed rule referenced a companion notice published elsewhere in the **Federal Register** of November 24, 2000 (65 FR 70573), reaffirming the new drug status of oral digoxin products and requiring approved applications for marketing. In that notice, FDA lifted the stay for submitting ANDAs for digoxin products for oral use.

II. Comments and the Agency's Response

Interested persons were given until February 22, 2001, to submit comments on the proposal. FDA received comments from four manufacturers of drug products subject to the proposal.

(Comment 1) Three of the four submitted comments agreed that the agency should revoke § 310.500. One comment identified several public health reasons to revoke § 310.500. Those reasons are described in section II of this document and incorporated into the agency's response to the one comment that opposed revocation of § 310.500.

A. Opposition to Proposed Rule

(Comment 2) One comment opposed the agency's proposed rule to revoke § 310.500, contending that the batch certification procedure is sufficient for FDA to regulate digoxin tablets and that the proposed rule is inadequate because FDA failed to identify a public health reason or change of facts or circumstances to justify revoking its regulation of digoxin tablets under batch certification.

FDA disagrees with this comment. The integrity of the batch certification process, the principal concern of the comment, is not the relevant issue. The relevant issue is whether the certification procedure is still warranted in light of new information or changing circumstances. FDA concludes it is not warranted and, as explained in section II of this document, has determined that revocation of § 310.500 is rationally related to FDA's statutory obligation to ensure that marketed oral digoxin drug products are safe, effective, and properly labeled as reflected by current scientific knowledge and information.

In its November 2000 proposed rule and a companion notice published in the same issue of the **Federal Register**, FDA described the reasons for the agency's plan to revoke § 310.500. As discussed in section II of this document, the agency believes those reasons are still valid and that revocation of the regulation is appropriate and required under the circumstances.

As noted in the proposed rule and companion notice, along with other prior notices referenced in the proposed rule, in 1974 FDA established the conditions for marketing oral digoxin drug products in § 310.500 because of safety concerns with digoxin products on the market. Studies had shown clinically significant differences in bioavailability of certain oral digoxin products. This variability was a major concern because of the drug's narrow therapeutic index and the potential

risk presented to patients using digoxin products of varying bioavailability. Therefore, FDA established the regulations to provide a systematic regulatory approach to ensure uniformity of marketed oral digoxin products.

The conditions for marketing included, among other things, requirements for submission of ANDAs, a batch certification program for digoxin tablets based on dissolution testing, and labeling requirements for all oral digoxin drug products. The requirement for ANDAs was later stayed pending resolution of the agency's ANDA policy. Absent submission of ANDAs, the batch certification program was the only preclearance requirement for digoxin tablets. The batch certification program was not intended to be a permanent solution to the problem of digoxin variability, but a stopgap measure to bring the potential for a serious health problem under control.

In that 1974 regulation, the agency also announced its determination that digoxin products for oral use are new drugs within the meaning of section 201(p) of the act (21 U.S.C. 321(p)). Because of the need for an optimal regulatory program to ensure the uniformity of oral digoxin drug products, FDA has, over the years, considered various approaches to bring digoxin into the new drug approval system.

The approval of NDA 20-405 for Lanoxin Tablets represented the first step in regulating all oral digoxin products under the requirements of section 505 of the act and the corresponding regulations. Approval of that NDA was also important because it provided data to help establish in vivo bioavailability and bioequivalence standards for oral digoxin drug products.

The approval of NDA 20–405 and the new information that emerged from the agency's review of the NDA provide a rational basis for the agency's actions to revoke § 310.500. Because the agency has approved an NDA for digoxin tablets, oral digoxin drug products are no longer covered by the exemptions set forth in Compliance Policy Guide (CPG) 7132c.02. That CPG provides priorities for regulating marketed new drugs without approved NDAs or ANDAs, such as oral digoxin products regulated under § 310.500.

As noted in one comment, FDA's decision to revoke § 310.500 is also supported by safety concerns related to the differences in labeling of the Lanoxin drug product and the labeling required under § 310.500. FDA approved NDA 20–405 for treatment of mild to moderate heart failure and for atrial fibrillation. The labeling of § 310.500 provides for use of digoxin in congestive heart failure (all degrees), atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, and cardiogenic shock.

The labeled indications for new drugs, such as oral digoxin drug products, must be supported by substantial evidence derived from adequate and well-controlled investigations, including clinical investigations. (See section 505(d) of the act (21 U.S.C. 355(d) and §§ 314.126, 201.56, and 201.57 (21 CFR 314.126, 201.56, and 201.57).) Labeling indications that are not supported by adequate and well-controlled studies are false and misleading, in violation of section 502(a) of the act (21 U.S.C. 352(a)).

Except for the data to support the two indications approved in NDA 20-405, the agency is not aware of any adequate and well-controlled studies to support the indications for use in § 310.500. Thus, the labeling of oral digoxin as set forth in § 310.500 is outdated and does not reflect current scientific and medical information about oral digoxin. Moreover, marketing of oral digoxin drug products with labeling described in § 310.500 could present a risk to patients because substantial scientific evidence to establish the safety and effectiveness of all of the indications in that labeling has not been established.

In addition, the criteria in § 310.500 are not current because the dissolution requirements specified in that regulation are no longer used as standards in the certification program. The dissolution requirements in § 310.500 differ from those in the current official U.S.P. monograph for oral digoxin tablets that FDA considers scientifically appropriate. Therefore, the dissolution requirements specified in § 310.500 for digoxin tablets are obsolete.

Furthermore, as described in a comment, § 310.500 lacks the uniform standards of the new drug approval system that ensure predictable bioavailability for oral digoxin products. Digoxin is

a potent drug with a narrow therapeutic index. Slight variations in bioavailability can result in toxicity or loss of effect. Formulation and manufacturing controls are critical to the safe and effective use of oral digoxin drug products. Review of oral digoxin through the new drug approval process is necessary to provide adequate evidence of safety and substantial evidence of effectiveness, as well as adequate information about formulation and manufacturing procedures.

In addition to approval requirements under the new drug approval system, all oral digoxin products must be subject to the same postmarketing requirements so that changes that may affect the safety or effectiveness of the products can be monitored. Sponsors of products not approved through the new drug approval process, such as oral digoxin products under § 310.500, may reformulate their products or make manufacturing changes without seeking FDA approval. Such changes may affect bioavailability and hence may affect the safety or effectiveness of the products.

Additionally, although manufacturers of such unapproved products are required under 21 CFR 310.305 to report adverse events that are serious and unexpected, they are not required to report all adverse events associated with drug use. In contrast, manufacturers of approved new drug products are required to report all adverse events under 21 CFR 314.80. Consequently, adverse drug events that may reflect problems with the safety or effectiveness of oral digoxin products may not be reported.

Moreover, allowing oral digoxin products to be marketed under § 310.500 and the new drug approval process creates confusion in the marketplace regarding the substitutability or interchangeability of the drug products. Products marketed under § 310.500 and those approved under the new drug approval system may have differences in bioavailability. Furthermore, marketed oral digoxin products cannot be considered to be therapeutically equivalent, and therefore substitutable, unless equivalence is demonstrated through appropriate bioequivalence studies. Regulating all oral digoxin drug products under the same approval process would eliminate those safety concerns.

As discussed in section I of this document and in the November 24, 2000, proposed rule and its companion notice published in the same issue of the **Federal Register**, the conditions established in § 310.500 for marketing oral digoxin products either are obsolete or no longer warranted. Because of the approval of the NDA for digoxin tablets and the new drug status of oral digoxin drug products, all oral digoxin products can and must be regulated under the new drug approval process for NDAs and ANDAs as set forth in section 505 of the act. Regulation through this process protects the public health by ensuring the safety and efficacy of each oral digoxin drug product. Therefore, the agency is revoking that regulation.

B. Requests for Extension of Time

As proposed, the final rule would become effective 30 days after its date of publication in the **Federal Register**.

(Comment 3) Three comments stated that additional time is needed to prepare, submit, and obtain approval of an NDA.

1. Digoxin Elixir

Two comments from manufacturers of digoxin elixir requested a 2-year compliance period. One comment, characterizing digoxin elixir as medically necessary, noted that there are only two manufacturers of digoxin elixir drug products and expressed concern that a shortage of digoxin elixir drug products may occur if such products were removed from the market 30 days after publication of the final rule in the **Federal Register**. The comment further indicated that preparation of an application for digoxin elixir is complicated by the fact that there is no reference listed drug for digoxin elixir in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book), and therefore, no guidance is currently available from the agency on which to base a submission for digoxin elixir drug products.

Digoxin elixir is a medically necessary dosage form. It is used primarily in the pediatric population for the treatment of atrial fibrillation and congestive heart failure, both serious and

potentially life-threatening diseases/conditions. Available alternative therapies are not approved for treating atrial fibrillation and congestive heart failure in the pediatric population. Such therapies are limited in their use because of toxicities, lack of safety and efficacy data in the pediatric population, and/or lack of a pediatric formulation allowing for consistent administration to children. There should not be a disruption in the marketplace for patients who need digoxin elixir. In order to protect the public health, FDA plans to exercise its enforcement discretion and not take regulatory action against currently marketed unapproved digoxin elixir products before [*insert date 2 years after date of publication in the* **Federal Register**]. This should allow sufficient time for a manufacturer to conduct the required tests, evaluate the data, and prepare and submit a new drug application to FDA. After that date, any digoxin elixir drug product on the market without an approved NDA or ANDA will be subject to regulatory action.

2. Digoxin Tablets

A manufacturer of digoxin tablets contends that FDA must extend the effective date of the final rule for at least 2 years to allow current producers and marketers of the drug products subject to the certification program to prepare, submit, and obtain an approved new drug application.

a. *Lack of notice*. In its comments, the manufacturer implies that the firm was not aware of FDA's intent to revoke § 310.500. (The comment's allegation that the proposed rule was issued to settle a lawsuit is spurious. The agency was preparing the proposed rule long before the party to that suit even approached the agency.)

The proposed rule itself provides reasonable notice of the agency's intent. The manufacturer has had more than a year in which to continue marketing under § 310.500 and, at the same time, pursue approval of an ANDA.

Moreover, a reasonably observant member of the drug industry would have known for a number of years that FDA intended to revoke § 310.500 and that applications approved through the new drug approval process would be required. For example, articles in the trade press have announced the agency's intention to require approval of oral digoxin through the new drug approval

process. (See e.g., F–D–C Reports, July 6, 1992 at 7.) NDA 20–405 for Lanoxin (digoxin) Tablets was approved in September 1997. The approval was published in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations," and also was reported in the trade press. (See e.g., *F–D–C Reports*, October 6, 1997 at T&G–2.) Certainly since that time, if not many years before, the drug industry has known that FDA would change its approach for regulating oral digoxin products and that the agency would take action to revoke § 310.500.

b. *Takings under the fifth amendment.* The manufacturer argues that if its digoxin drug product is removed from the market 30 days after publication of the final rule in the **Federal Register**, the potential loss to its company would be substantial and could constitute a "taking" for which the Federal Government could be financially liable. The manufacturer did not submit any evidence or analysis to support its views.

FDA disagrees that this final rule effects a taking in violation of the fifth amendment of the United States Constitution. The Supreme Court has developed three factors to consider in assessing whether a regulatory taking has occurred: (1) The character of the governmental action, (2) its economic impact, and (3) its interference with reasonable investment-backed expectations. (See *Ruckelshaus* v. *Monsanto Co.*, 467 U.S. 986, 1005 (1984).)

The force of any one of these factors may be "so overwhelming * * * that it disposes of the taking question" (*Ruckelshaus*, 467 U.S. at 1005) (finding interference with reasonable investment-backed expectations by use of trade secret information in pesticide approval process to be decisive). So, for example, if the economic impact is to rob real property of "all economically beneficial uses," the regulation effects a taking (*Lucas* v. *South Carolina Coastal Council*, 112 S. Ct. 2886, 2899 (1992) emphasis in original). Regulations that cause a temporary denial of property use, however, are not subject to such "per se" rules but entail complex factual assessments of the purposes and economic effects of government actions. See *Tahoe-Sierra Preservation Council* v. *Tahoe Regional Planning Agency*, No. 00–1167, 2002 WL 654431 (U.S. April 23, 2002).

When examined in light of these three factors, FDA's revocation of § 310.500 clearly does not effect a compensable taking under the fifth amendment of the Constitution.

i. *Character of the governmental action.* With respect to the first factor, courts are more likely to find a taking when the interference with property can be characterized as a physical invasion by the Government (e.g. *United States* v. *Causby*, 328 U.S. 256, 261–62 (1946) (characterizing Government's use of flight path just over property as physical invasion)) than when the interference is caused by a regulatory program that "adjust[s] the benefits and burdens of economic life to promote the common good." (*See Penn Central Transp. Co. v. City of New York*, 438 U.S. 104, 124 (1978).) Courts have accorded particular deference to governmental action taken to protect the public interest in health, safety, and welfare. (See *Keystone Bituminous Coal Ass'n* v. *DeBenedictis*, 480 U.S. 470, 488 (1987).)

In this case the governmental action is associated with a regulatory program designed to protect the health and safety of the public. Revocation of § 310.500 is intended to ensure that digoxin drug products on the market meet the current safety and efficacy product approval standards and are regulated in the same manner as other drug products under the act. As such, it does not constitute governmental action that would be considered a taking.

ii. *Economic impact.* The second factor to consider is the economic impact of the governmental action. "There is no fixed formula to determine how much diminution in market value is allowable without the fifth amendment coming into play" (*Florida Rock Indus., Inc.* v. *United States*, 791 F.2d 893, 901 (Fed. Cir. 1986), cert. denied, 479 U.S. 1053 (1987)). It is clear, however, that a regulation's economic impact may be great without rising to the level of a taking. (*See Pace Resources Inc.* v. *Shrewsbury Township*, 808 F.2d 1023, 1031 (3d Cir.), cert. denied, 482 U.S. 906 (1987) (no taking even given reduction in value from $800,000 to $60,000); *Village of Euclid* v. *Ambler Realty Co.*, 272 U.S. 365 (1926) (no taking despite 75 percent diminution in value).) Mere denial of the most profitable or beneficial use of property does not require a finding that

a taking has occurred. (*See Florida Rock Indus., Inc.* v. *United States*, 791 F.2d 893, 901 (Fed. Cir. 1986), cert. denied 479 U.S. 1053 (1987); see also *Andrus* v. *Allard*, 444 U.S. 51, 66 (1979).)

In assessing whether a regulation effects a taking, the Supreme Court has considered whether the regulation denies an owner the "economically viable" use of its property. See, e.g., *Keystone*, 480 U.S. at 499. This analysis involves looking not just at what has been lost, but at the whole "bundle" of property rights. *Andrus* v. *Allard*, 444 U.S. at 65–66. Courts focus on the remaining uses permitted and the residual value of the property. *Pace Resources*, 808 F.2d at 1031. Although it is undeniable that compliance with these regulations will cost money and may mean that certain product names must be altered, companies will not be denied the economically viable use of their property.

By revoking the regulation, the agency is not taking away the ability of manufacturers to market digoxin drug products. The one manufacturer that might be affected does not complain in its comments that it would be unable to produce digoxin, but that it would face "severe difficulty re-entering the market and re-establishing its position after an absence which could span a year or more while waiting for FDA to approve an NDA or ANDA." The manufacturer may submit an NDA or ANDA and then market its digoxin drug product after approval. It is possible that this could be done with little or no interruption in marketing. Therefore, the manufacturer has "remaining uses" of its property and does not suffer loss of "economically viable use" of property. (*See Pace Resources*, 808 F. 2d at 1031; and Keystone, 480 U.S. at 499.) Consequently, this factor also does not support a conclusion that revocation of the regulatory provision is a taking.

iii. *Investment-backed expectation.*The final factor to consider is whether a company has a reasonable investment-backed expectation in continuing to use the property at issue. To be reasonable, expectations must take into account the power of the State to regulate in the public interest. (*See Pace Resources*, 808 F.2d at 1033.) Reasonable expectations must also take into account the regulatory environment, including the foreseeability of changes in the regulatory scheme. "In an industry that long has been the focus of great public concern and significant

government regulation," *Monsanto*, 467 U.S. at 1008, the possibility is substantial that there will be additional regulatory requirements. "Those who do business in the regulated field cannot object if the legislative scheme is buttressed by subsequent amendments to achieve the legislative end." (*See Connolly* v. *Pension Benefit Guarantee Corp.*, 475 U.S. 211, 227 (1986).)

The manufacturer is a regulated body and, as such, has been aware from the time it began manufacturing digoxin that the regulatory scheme could be modified. As described in section II.B.2.a of this document, the manufacturer has had notice for many years that the regulatory scheme in § 310.500 would be changed. As with the other factors, analysis of this factor establishes that revoking § 310.500 is not a taking under the fifth amendment.

When examined in light of these three factors, FDA's revocation of § 310.500 clearly does not effect a compensable taking under the fifth amendment of the Constitution.

c. *Market disruption.* Contrary to the comment's assertion, FDA does not believe that a disruption in the marketplace of digoxin tablets will occur if, should it be necessary, an unapproved digoxin tablet product supplying from 15 to 20 percent of the market is taken off the market. As the comment recognizes, there are two other manufacturers of digoxin tablets, holders of approved NDAs. FDA believes that these manufacturers are capable of satisfying an increased demand for digoxin tablets.

d. *Levothyroxine sodium.* In further support of its contention that FDA extend the effective date of the final rule, the comment alleges that the digoxin tablet drug products are in a situation similar to that in which sponsors of levothyroxine sodium were allowed a minimum of 3 years to obtain approved NDAs. The comment contends that FDA should accord comparable time for completion and review of digoxin NDAs.

The agency's handling of levothyroxine sodium does not provide a necessary precedent for setting an effective date for approval of digoxin tablet drug products. The facts involving digoxin tablets and levothyroxine sodium differ in at least two significant ways. First, the **Federal Register** notice of August 14, 1997 (62 FR 43535) (announced that orally administered drug products

containing levothyroxine sodium are new drugs and announced the conditions for marketing the products), was the first time FDA issued any public announcement of the new drug status of levothyroxine sodium products. By contrast, in the **Federal Register** of November 24, 2000 (65 FR 70573), FDA reaffirmed the agency's 1974 determination that digoxin products for oral use are new drugs requiring approved NDAs. Second, and most importantly, when FDA published the notice on levothyroxine sodium drug products, there were no approved NDAs for the products. When FDA published the proposed rule on digoxin, on the other hand, there were two approved products on the market for digoxin tablets under NDA 20–405 and ANDA 40–282. Because FDA determined that levothyroxine sodium drug products are medically necessary, sponsors of the products were allowed 3 years to obtain approved NDAs. In contrast, while digoxin tablets may be medically necessary, there is no medical necessity for unapproved digoxin tablets. Unapproved digoxin tablets may be indicated for serious cardiac conditions, as the comment claims, but there are approved digoxin tablets in sufficient quantity to meet the market demand.

To summarize, the comment has set forth no sufficient reason to justify an extension. Industry has been on notice for a number of years that § 310.500 would be revoked and that applications approved through the new drug procedures would be required. It is the manufacturer's responsibility to prove the safety and effectiveness of its product(s).

III. Implementation Plan

A. Digoxin Elixir

In order to protect the public health, FDA plans to exercise its enforcement discretion and not take regulatory action against currently marketed unapproved digoxin elixir products before [*insert date 2 years after date of publication in the* **Federal Register**]. Any unapproved digoxin elixir introduced after [*insert date of publication in the* **Federal Register**], will be subject to regulatory action when this rule becomes effective on [*insert date 30 days after date of publication in the* **Federal Register**].

B. Digoxin Tablets

Any unapproved digoxin tablet will be subject to regulatory action when this rule becomes effective on [*insert date 30 days after date of publication in the* **Federal Register**].

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize the benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize any significant impact of a rule on small entities.

The agency has reviewed this final rule and determined that it is consistent with the regulatory philosophy and principles identified in the Executive order and these two statutes. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for the final rule because the final rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation-adjusted statutory threshold is $110 million. No further analysis is required under the Regulatory Flexibility Act because the agency has determined that this final rule will not have a significant effect on a substantial number of small entities.

As mentioned in the proposed rule, several studies have indicated a significant variation in the bioavailability of digoxin products for oral use. FDA published the January 1974 regulation that established conditions for marketing such products, including a mandatory batch certification program for digoxin tablets. In the proposed rule, FDA described actions that have occurred since that regulation was published that render the January 1974 regulation unnecessary. Therefore, under this final rule, manufacturers of digoxin products will be required to obtain an approved marketing application to enter or remain on the market.

In the proposed rule, FDA noted that one of the manufacturers of digoxin tablets had not already obtained an NDA or ANDA and would need to obtain an ANDA to remain on the market. In addition, the two manufacturers of digoxin elixir would need to obtain approved applications. In the proposed rule, the agency calculated a cost of submitting either an ANDA or 505(b)(2) application, based on an estimate of 480 hours to complete the necessary paperwork.

One comment disagreed with the estimate of 480 hours, contending it to be a gross underestimate of the actual time required. The comment did not provide an alternate estimate. It should be noted that the estimate in the proposed rule considered that the three manufacturers in question would be submitting an application to market a dosage form they were already producing. Nevertheless, the agency acknowledges that the 480-hour figure may underestimate the actual time required. Accordingly, for this final rule, the agency estimates the time to complete an ANDA or 505(b)(2) application to be between 480 and 720 hours.

Using a 2001 labor rate of $49 per hour[1], and assuming 480 to 720 hours to complete the required application, the one-time cost is between $23,500 and $35,300 ($49/hour x 480 to 720 hours). The one-time cost to all three firms is between $70,600 and $105,800 (3 x $23,500 to $35,300).

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[1]U.S. Department of Labor, Bureau of Labor Statistics, "2001 Occupational Earnings Data," Lawyer: FTP:/ /ftp.bls.gov/pub/special.requests.1f/aat39.txt, 1 February 2002.

As stated in the proposed rule, FDA recognizes there will be future submission costs for new manufacturers of digoxin for oral use, and estimates two manufacturers will enter the market per decade. Some additional annual costs may also be incurred over the life of the application. While there may be some cost savings from the elimination of the batch certification requirement, the savings will be negligible.

According to the Small Business Administration, manufacturers of pharmaceutical preparations with 750 or fewer employees are considered small entities. Applying this definition, only one of the four current manufacturers that will incur submission costs is a small entity. In addition, these costs are likely to represent less than 1 percent of gross revenue. Therefore, the agency certifies that this action will not have a significant economic effect on a substantial number of small entities.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

This final rule does not require information collection subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (Public Law 104–13). The information collection consists of the submission of NDAs or ANDAs for digoxin products for oral use. The information collection requirements for the submission of NDAs and ANDAs are contained in 21 CFR part 314 and have been approved under OMB control number 0910–0001, which expires on March 31, 2005.

List of Subjects for 21 CFR Part 310

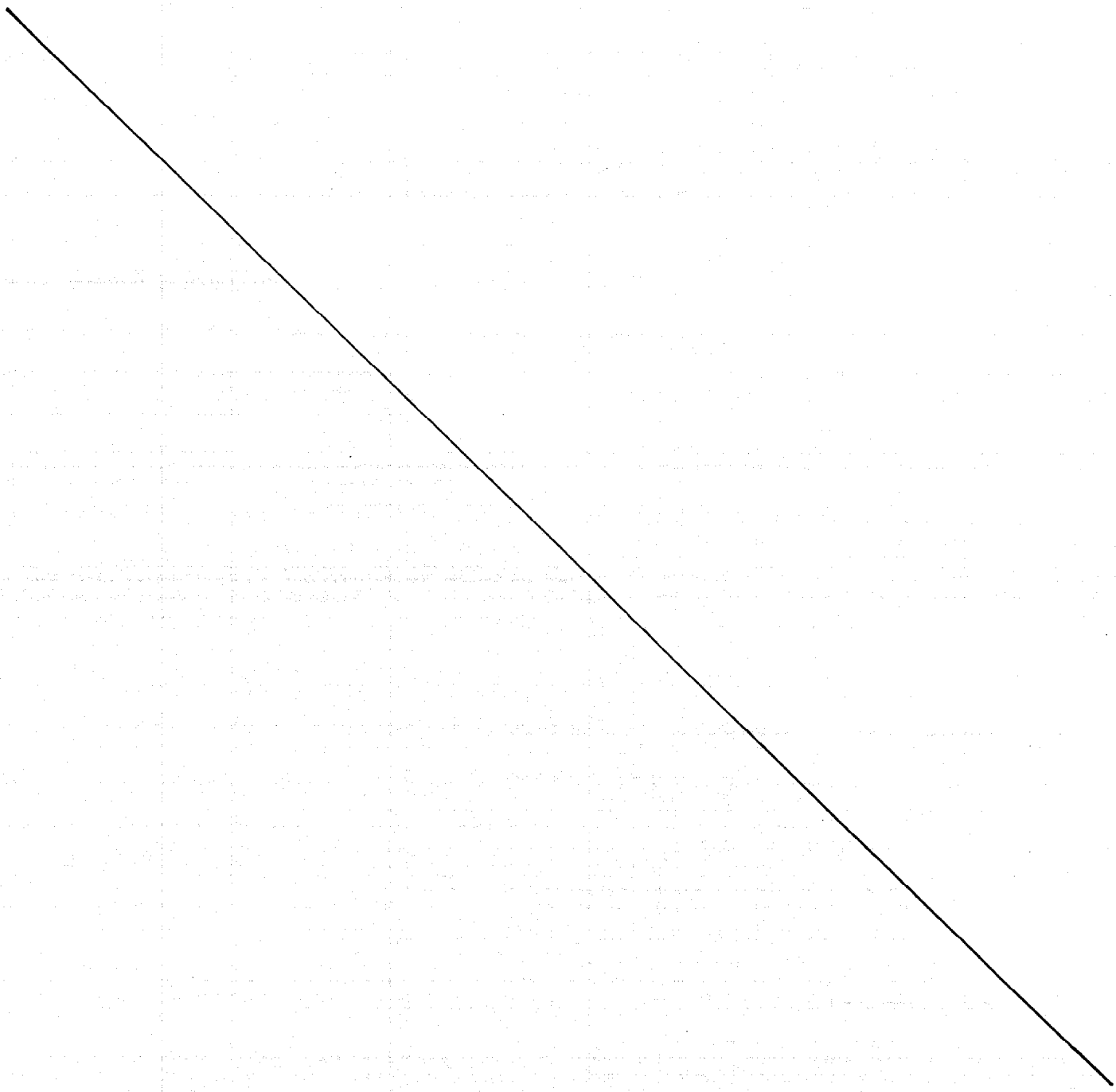
Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.



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6/20/02

§ 310.500 [Removed]

2. Section 310.500 *Digoxin products for oral use; conditions for marketing* is removed.

Dated: 6/17/02

June 17, 2002.

Margaret M. Dotzel,
Associate Commissioner for Policy.

[FR Doc. 02–????? Filed ??–??–02; 8:45 am]

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